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Oxygen–chlorine interactions in the transition state of asymmetric Michael additions of carbonyl compounds to β-nitrostyrene

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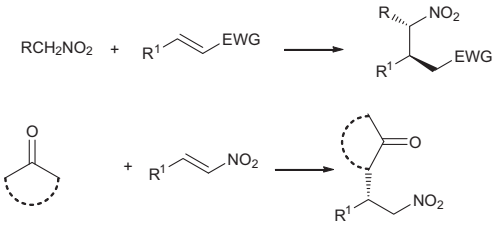
ABSTRACT

An oxygen–chlorine interaction is reported in the transition state of the Michael addition of acetone to nitrostyrene catalyzed by enantioenriched monosulfonamides. The interaction between the oxygen from the nitro group and the chlorine at the *ortho*-position of the sulfonamide moiety is supported by theoretical calculations. Asymmetric Michael addition products catalyzed by monosulfonamides were obtained in moderate yields and enantioselectivities.

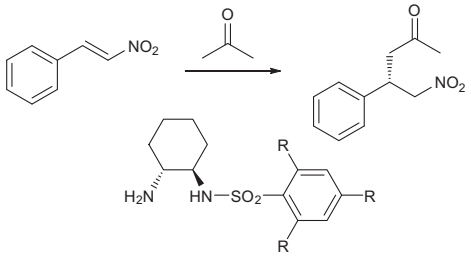
1. Introduction

The catalytic Michael reaction is an important and well-studied process for stereoselective carbon–carbon bond formation in organic synthesis.[1] In recent years, the field of asymmetric organocatalytic Michael reactions has received widespread attention.[2] Among the reactions studied, the conjugate addition of nitroalkanes to α,β-unsaturated systems and additions involving carbonyl compounds to α,β-unsaturated nitroalkenes are of great interest (Scheme 1).[3,4] The products obtained are direct precursors to important structural moieties, such as γ-aminocarbonyls, 2-pyrrolidones, and 2-piperidones.[3a]



Scheme 1. Michael addition of nucleophiles to α,β-unsaturated systems with an electron-withdrawing group.

Various classes of bifunctional organocatalysts have been employed in Michael additions, such as thioureas, cinchona alkaloids, proline derivatives, and sulfonamides.[4a] Having a library of enantioenriched monosulfonamides in hand,[5] we turned our attention to using these ligands as organocatalysts in Michael additions. Herein we report the use of enantioenriched mono-sulfonamides derived from (1*R*,2*R*)-cyclohexanediamine as bifunctional organocatalysts to promote the addition of carbonyl compounds to β-nitrostyrene (Scheme 2).



Scheme 2. Michael addition of acetone to nitrostyrene catalyzed by chiral monosulfonamides.

The sulfonamide organocatalyst acts as a weak hydrogen bond donor, and at the same time contains a basic primary amino group that can activate the nucleophilic reaction partner (in this case, acetone) by generation of an enamine. Thus, the catalyst is proposed to be bifunctional in the transition state of the reaction (Fig. 1A).

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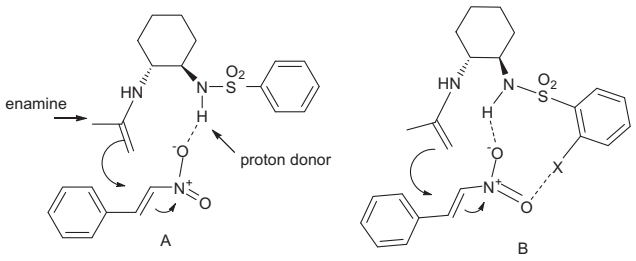


Figure 1. Proposed transition states in the Michael addition of acetone to nitrostyrene.

In addition to the hydrogen donor interactions, we report, for the first time, a novel O···Cl interaction and its participation in the stabilization of the transition state for the Michael addition reaction (Fig. 1B, X = Cl). Similar O···Cl interactions have been reported in the X-ray crystal structure of 2,5-dichloro-1,4-benzoquinone (Fig. 2).[6] Non-covalent interactions between electron-deficient halogen compounds and Lewis bases (O, N) have gained recognition as a useful class of interactions, similar to hydrogen bonding, and have recently been christened 'halogen bonds'.[7] Similar interactions have been reported for supramolecular assemblies in medicinal chemistry and in crystalline assemblies.[6,8–13]

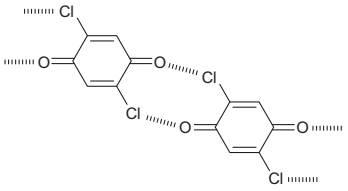
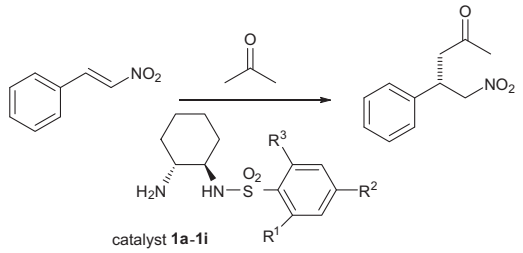


Figure 2. O···Cl interaction in the 2,5-dichloro-1,4-benzoquinone crystal structure.

2. Results and discussion

Enantioenriched monosulfonamides **1a**–**1i** were synthesized using a previously reported method,[14] and tested in the Michael addition reaction. The results in Table 1 show an interesting effect:

Table 1
Monosulfonamides **1a**–**1i** evaluated in the Michael addition of acetone to nitrostyrene[a]



Catalyst	Yield[b] (%)	ee[c] (%)
1a) $R^1 = R^2 = R^3 = H$	78	75
1b) $R^1 = R^3 = H$, $R^2 = CH_3$	86	76
1c) $R^1 = R^3 = H$, R^2 = *tert*-butyl	80	79
1d) $R^1 = R^2 = R^3 = CH_3$	85	72
1e) $R^1 = R^2 = R^3$ = *iso*propyl	No product	—
1f) $R^1 = R^3 = H$, $R^2 = NO_2$	78	61
1g) $R^1 = R^3 = H$, $R^2 = CF_3$	85	77
1h) $R^1 = R^3 = H$, $R^2 = CN$	80	78
1i) $R^1 = R^3 = H$, $R^2 = I$	86	74

[a] All entries are for 10 mol % in toluene over 5 days.
[b] Yields were determined by HPLC with a Chiralpak AS-H column at 208 nm (hexane/*i*-PrOH75:25, 1 mL/min).
[c] The enantiomeric excesses were determined by HPLC and the absolute configuration was established as (*R*), and assigned by comparing the t_R with literature values.[15]

going from the *ortho*-substituents R = H **1a**–**c** and R = CH_3 **1d** to R = *iso*propyl **1e** on the sulfonamide aryl ring, the reaction was quenched. The bulky substituent in the sulfonamide (2,4,6-*i*-$Pr_3C_6H_2$ in **1e**) induced strong steric repulsions between nitrostyrene and the substituted sulfonyl group, which diminishes the hydrogen bonding interactions, and leads to a very slow reaction rate. Furthermore, electron-withdrawing groups on the sulfonamide aryl ring **1f**–**i** had very little impact on the yield and enantioselectivity.

Based on this observation, our intention was to transform this steric repulsion into an electronic attraction by replacing the isopropyl group with a proton donor group at the *ortho* position of the sulfonamide aromatic ring. Our expectation was that both oxygens of the nitro group would now be hydrogen-bonded to the ligand (Fig. 1B). The double oxygen interaction might then stabilize the transition state and enhance the enantioselectivity. An obvious choice for group X is —OH. Thus, we synthesized the monosulfonamide **2** (Fig. 3), and tested it in the Michael addition of acetone to nitrostyrene in toluene. The addition product was obtained with excellent enantioselectivity (>98%), although only 33% yield. We considered this low yield was perhaps due to the lack of solubility of organocatalyst **2** in the solvent used in the reaction (toluene). As predicted, changing the solvent to anhydrous polar aprotic DMSO, led to a lower ee (40%), probably due to disruption of the hydrogen bonding in the transition state.

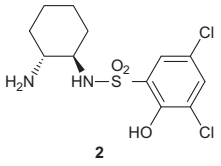
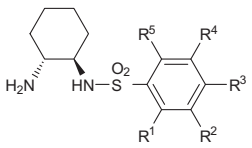


Figure 3. Monosulfonamide 2 with a phenolic OH as a proton donor.

Looking for an alternate, more soluble functionalized sulfonamide, our literature search revealed a report by Allen et al. on novel intermolecular interactions between halogens and oxygen or nitrogen.[6] The authors observed an intermolecular Cl···O interaction in the X-ray structure of 2,5-dichloro-1,4-benzoquinone, similar to hydrogen bonding (Fig. 2). Their proposal was supported by theoretical calculations, suggesting that a general halogen (Cl, Br, I)-oxygen or nitrogen bond interaction could have bond energy comparable to that of O···H hydrogen bonding. More recently, Jacobsen reported on an iodonium ion-nitrogen interaction in the transition state leading to an enantioselective iodolactonization reaction.[16] This encouraged us to synthesize a series of ligands with an *o*-chlorine substituent and apply them as organocatalysts in the 1,4-addition reaction, with the idea that the O···Cl interaction, seen in the benzoquinone crystal structure, would be mimicked in the transition state of the Michael addition shown in Fig. 1B. Various halogenated monosulfonamides **3a**–**e** were synthesized from commercially available sulfonyl chlorides (Fig. 4) and tested in the asymmetric addition of acetone to nitrostyrene. The results are shown in Table 2.



3a) $R^1 = R^2 = Cl$, $R^3 = R^4 = R^5 = H$
3b) $R^1 = R^3 = Cl$, $R^2 = R^4 = R^5 = H$
3c) $R^1 = R^4 = Cl$, $R^2 = R^3 = R^5 = H$
3d) $R^1 = R^5 = Cl$, $R^2 = R^3 = R^4 = H$
3e) $R^1 = R^4 = Br$, $R^2 = R^3 = R^5 = H$

Figure 4. Halogenated monosulfonamides.

Table 2
Monosulfonamides **3a**–**3e** evaluated in the Michael addition of acetone to nitrostyrene[a]

Catalyst	Yield[b] (%)	ee (%)[c]
3a	96	84
3b	97	81
3c	96	85
3d	99	88
3e	86	88

[a] All entries are for 10 mol % in toluene over 5 days.
[b] Yields were determined by HPLC with a Chiralpak AS-H column at 208 nm (hexane/*i*-PrOH75:25, 1 mL/min).
[c] The enantiomeric excesses were determined by HPLC and the absolute configuration was established as (*R*), and assigned by comparing the t_R with literature values.[15]

The results indicated a positive increase in the enantioselectivities (8–17%) and yields (8–26%) compared to the unsubstituted benzene sulfonamide (Table 1, entry **1a** and Table 2). Although no dramatic enhancement in the enantioselectivities was seen, this notable increasing trend led us to carry out theoretical calculations on the transition states involving ligands **3a**–**d** to probe the experimental observations. Calculations using Gaussian 09[17] were carried out for monosulfonamides **3a**–**3d** (also **2**) using the B3LYP density functional theory[18] and the cc-pVDZ basis set.[19]

Table 3 shows the relevant atom–atom distances for the *PRO-S* transition state with the organocatalyst **3a**–**3d** (values for the *PRO-R* was similar). The distance C—C was 1.93 Å, and NO—H was 1.966 to 2.044 Å.

Table 3
DFT computed distances (Å) of interactions in the *PRO-S* transition states and *R*–*S* relative energies (kcal/mol) of Michael reactions

Catalyst	C—C	O—H	O—Cl	X—OS[b]	$\Delta\Delta G^{\neq}$ TS
3a	1.93	1.966	3.470[a]	2.318	−0.670
3b	1.93	2.009	3.365	2.362	−1.680
3c	1.94	2.025	3.391	2.36	−3.105
3d	1.93	2.044	3.421	2.873	−2.283

[a] Interaction with Cl on R^2.
[b] X = H in **3a**–**3d** and Cl in **3d**.

The calculations predict a Cl···O interaction involving the nitro group O-atom, with separation distances of 3.391 to 3.470 Å. The energy of the interaction between the oxygen and the chlorine was obtained by comparing the energies of the distinct transition state conformers of **3c**. By fixing several dihedral angles to separate the O and Cl atoms by more than 5 Å, we estimated the energy of the transition state in the absence of the O and Cl interaction. The O···Cl interaction energy was estimated to be 2.32 kcal/mol in the *PRO-S* TS by these means, and 1.61 kcal/mol in *PRO-R* TS. The higher energy for the O···Cl interaction was found for the PRO-S transition state, consistent with experimental results, where the (*S*)-enantiomer is obtained in all Michael reactions that use sulfonamide organocatalysts **3a**–**3d** containing a Lewis-acidic chlorine.

An interaction was also found between the sulfonamide and the *o*-hydrogen (in the case of **3d** with chlorine) of the benzenoid ring of the sulfonamide (Table 3), with separation distances from 2.318 to 2.873 Å, with a roughly periplanar conformation (Fig. 5).

Two oxygen bonding interactions (O···H and O···Cl), as shown in Figure 6A, were found in the more favored *PRO-S* transition state for all cases with organocatalyst **3a**–**3d**, in contrast to a single oxygen interaction with both H and Cl in the unfavored *PRO-R* transition state as shown in Figure 6B, except for **3c**.

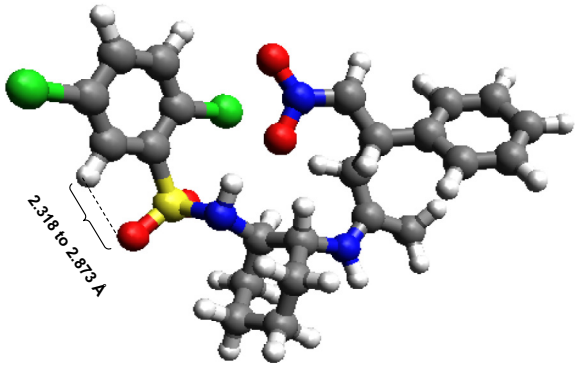


Figure 5. Interaction between the sulfoxide oxygen and the *o*-hydrogen of the dichlorophenyl group.

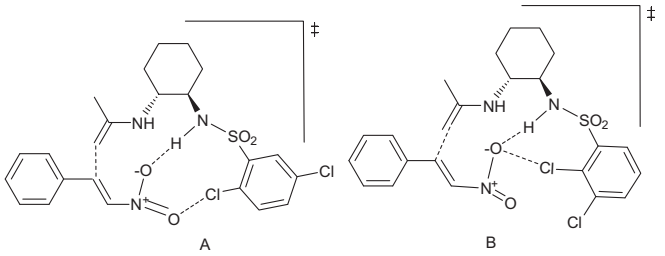


Figure 6. Transition state of (A) *PRO-S* 3c; (B) *PRO-R* **3a**.

With respect to organocatalyst **2**, an evident NO···HO interaction was predicted by the DFT calculations, with a separation of 1.697 Å, and the NO-HN separation was predicted to be 2.42 Å (Fig. 7). The $\Delta\Delta G^{\neq}$ of the transition state (*S*–*R*) was equal to −3.29 kcal/mol. This result was in agreement with the high enantioselectivity obtained experimentally.

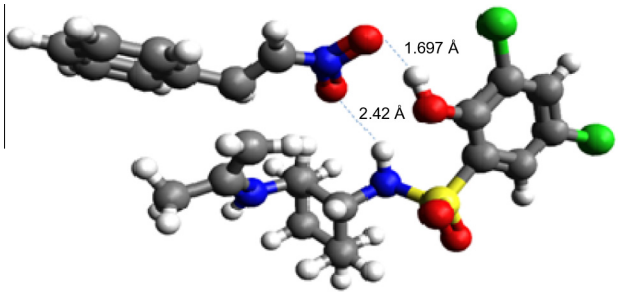


Figure 7. NO···HN and NO···HO interaction distances in the transition state of **2**.

Comparing the transition state in the thiourea-catalyzed Michael addition, Tsogoeva et al. suggested from calculations that the double hydrogen bonding of the two thiourea NHs to a single NO_2 oxygen is the favored transition state[20] (Fig. 8A). Based on this

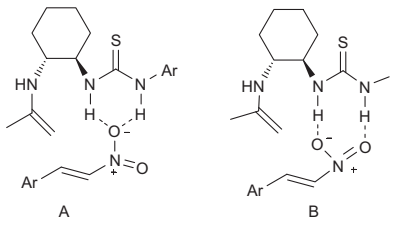


Figure 8. Transition states involving a thiourea organocatalyst, (A) favored; (B) unfavored.[20]

reasoning, the lack of enantioselectivity enhancement may be explained by the double oxygen (NO_2) bonding from the nitro group to the NH and the chlorine of the ligands **3a–e** (Fig. 6A), which may not offer a favorable orientation of the alkene for nucleophilic attack.[21] This unfavorable orientation would affect the enantioselectivity, but not the yield.

3. Conclusion

In conclusion, we have demonstrated an unprecedented example of an O···Cl interaction in the transition state of the Michael addition of acetone to a nitroolefin as catalyzed by bifunctional monosulfonamides, providing Michael adducts in moderate yields and enantioselectivities. Our finding is supported by theoretical calculations. This subtle O···Cl attraction and similar interactions may play a role in the future design of bifunctional or multifunctional O···Cl organocatalysts.

4. Experimental section

4.1. General procedure for the preparation of the monosulfonamides

To a stirred solution of the L-tartrate salt of (*R*,*R*)-1,2-diaminocyclohexane (5.0 g, 18.9 mmol) in 35 mL of a 2 M NaOH solution, were added 5.3 mL of NEt_3 and 100 mL of CH_2Cl_2. The mixture was cooled to 0 °C and a solution of the corresponding arylsulfonylchoride (13 mmol) in 50 mL of CH_2Cl_2 was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was extracted with a 2 M HCl solution (3 × 100 mL). The aqueous phase was basified with 2 M NaOH solution, and extracted with CH_2Cl_2 (3 × 75 mL). The solvent was removed under reduced pressure and the corresponding product was purified by either column chromatography over silica gel or recrystallization.

Monosulfonamides **1a–i** were synthesized using a previously reported method and the spectroscopic data were in good agreement with those reported in the literature.[14]

4.1.1. *N*-((1*R*,2*R*)-2-Aminocyclohexyl)-3,5-dichloro-2-hydroxybenzenesulfonamide 2

This compound was obtained as a white solid with a yield of 69% (2.70 g, 7.9 mmol). Mp 304–305 °C, IR: 3372 (OH), 3213 (NH), 3027 (C—H, Ar), 2947 (CH, Alif), 1441 (C=C, Ar), 1298, 1138 (SO_2) cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 7.25 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 5.20 (br s, OH), 3.2 (m, NH), 2.65 (m, 1H), 2.45 (m, 1H), 1.82 (m, 1H), 1.50 (m, 1H), 1.40–1.00 (m, 6H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 161.9, 132.2, 127.4, 127.3, 126.5, 109.6, 53.2, 46.0, 34.0, 30.0, 24.5, 24.0; EIMS m/z: $[M]^+$ 338 (3), 177 (3), 133 (15), 113 (57), 96 (100), 56 (19).

4.1.2. *N*-((1*R*,2*R*)-2-Aminocyclohexyl)-2,3-dichlorobenzenesulfonamide 3a

This compound was obtained as a white solid with a yield of 44% (1.80 g, 5.57 mmol). Mp 98 °C, $[\alpha]_D^{20} = -20$ (c 0.72, CH_2Cl_2), IR: 3354, 3288 (NH_2), 3081 (C—H, Ar), 2932 (CH, Alif), 2859 (C—C), 1591, 1436, 1400 (C=C, Ar), 1327, 1160 (SO_2), 1090, 1048 (S=O), 914 (NH, tors), 834–706 (C—Cl) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, J = 7.8 Hz, 1H), 7.66 (dd, J = 7.8 Hz, 1H), 7.37 (t, J = 7.8 Hz 1H), 3.6–3.2 (m, 3H, NH), 2.81 (m, 1H), 2.62 (m, 1H), 2.02 (m, 1H), 1.70 (m, 1H), 1.65 (m, 1H), 1.59 (m, 1H), 1.20 (m, 3H), 1.10 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 140.6, 135.4, 134.3, 130.0, 129.3, 127.5, 60.3, 54.7, 34.6, 32.1, 24.8, 24.5; EIMS m/z: $[M]^+$ 297 (2), 267 (9), 189 (27), 113 (69), 96 (100), 43 (85); Calcd for $C_{12}H_{16}Cl_2N_2O_2S$: C, 44.59; H, 4.99. Found: C, 44.66; H, 5.04.

4.1.3. *N*-((1*R*,2*R*)-2-Aminocyclohexyl)-2,4-dichlorobenzenesulfonamide 3b

This compound was obtained as a white solid with a yield of 90% (3.7 g, 11.43 mmol). Mp 136 °C; IR: 3351, 3289 (NH_2), 3099 (C—H, Ar), 2945, 2928 (CH, Alif), 2859 (C—C), 1573, 1555, 1457, 1373 (C=C, Ar), 1323, 1161 (SO_2), 1076, 1040 (S=O), 836–815 (C—Cl) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.39 (dd, J = 8.4, 2.4 Hz 1H), 3.2–2.7 (s, 3H, NH), 2.67 (m, 1H), 2.46 (m, 1H), 1.95 (m, 1H), 1.77 (m, 1H), 1.63 (m, 2H), 1.22 (m, 2H), 1.09 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.3, 137.0, 132.6, 132.0, 131.4, 127.5, 60.9, 54.8, 35.3, 32.3, 24.9, 24.6; EIMS m/z: $[M]^+$ 323 (1), 145 (30), 113 (91), 96 (100), 79 (51), 56 (70); Calcd for $C_{12}H_{16}Cl_2N_2O_2S$: C, 44.59; H, 4.99. Found: C, 44.71; H, 5.12.

4.1.4. *N*-((1*R*,2*R*)-2-Aminocyclohexyl)-2,5-dichlorobenzenesulfonamide 3c

This compound was obtained as a green solid with a yield of 60% (3.7 g, 11. 36 mmol). Mp 143 °C; $[\alpha]_D^{20} = -29$ (c 1.1, MeOH); IR: 3361, 3298 (NH_2), 3094 (C—H, Ar), 2949 (CH, Alif), 2842 (—C—), 1582, 1451, 1441, 1376 (C=C, Ar), 1324, 1160 (SO_2), 1074, 1041 (S=O), 827-678 (C—Cl) cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 8.01 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.68 (dd, J = 8.4, 2.4 Hz 1H), 4.1 (s, 3H, NH), 2.7 (td,, 9.6, 4.2 Hz 1H), 2.44 (td, J = 9.6, 4.2 Hz, 1H), 1.75 (m, 2H), 1.55 (m, 2H), 1.24–0.98 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6)): δ 141.0, 133.9, 132.4, 130.3, 129.9, 60.5, 54.0, 33.9, 32.6, 24.9, 24.6; EIMS m/z: $[M]^+$ 323 (1), 145 (10), 113 (90), 96 (100), 79 (66), 56 (58), 43 (25); Calcd for $C_{12}H_{16}Cl_2N_2O_2S$: C, 44.59; H, 4.99. Found: C, 44.63; H, 5.03.

4.1.5. N-((1*R*,2*R*)-2-Aminocyclohexyl)-2,6-dichlorobenzenesulfonamide 3d

This compound was obtained as a white solid with a yield of 55% (2.2 g, 6.9 mmol). Mp 130 °C; $[\alpha]_D^{20} = -30$ (c 0.84, CH_2Cl_2); IR: 3354, 3292 (NH_2), 3031 (C-H, Ar), 2944, 2921 (CH, Alif), 2860 (-C-C-), 1594, 1571, 1560, 1425 (C=C, Ar), 1331, 1165 (SO_2), 1076, 1045 (S=O).cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, J=8.1 Hz, 2H), 7.33 (t, J = 8.1 Hz, 1H), 3.80-3.00 (s, 3H, NH), 2.90 (td, J=10.2, 3.8 Hz, 1H), 2.55 (td, J = 10.7, 3.8 Hz, 1H), 2.01 (m, 1H), 1.79 (m, 1H), 1.65 (m, 2H), 1.20 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.5, 134.9, 132.2, 131.4, 60.8, 54.7, 35.0, 32.0, 24.8, 24.7; EIMS m/z: $[M]^+$ 323 (7), 145 (20), 113 (92), 96 (100), 79 (45), 56 (64), 43 (45) ; Calcd. for $C_{12}H_{16}Cl_2N_2O_2S$: C, 44.59; H, 4.99. Found: C, 44.60; H, 5.02.

4.1.6. *N*-((1*R*,2*R*)-2-Aminocyclohexyl)-2,5-dibromobenzenesulfonamide 3e

This compound was obtained as a white solid with a yield of 85% (3.6 g, 10.75 mmol). Mp 163 °C; $[\alpha]_D^{20} = -17$ (c 6.1, MeOH); IR: 3354, 3294 (NH_2), 3092 (Ar-H), 2943 (CH, Alif), 2839 (C—C), 1584, 1475, 1442, 1369 (C=C, Ar), 1323, 1159 (SO_2), 1071, 1022 (S=O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.28 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.4, 2.4 Hz 1H), 2.70 (m, 1H), 2.43 (m, 1H), 1.95 (m, 1H), 1.79 (m, 1H), 1.66 (m, 2H), 1.30–1.04 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.6, 136.4, 136.3, 133.9, 121.7, 118.6, 61.1, 54.9, 35.3, 32.3, 24.9, 24.7; EIMS m/z: $[M]^+$ 412 (1), 113 (92), 96 (100), 79 (19); Calcd for $C_{12}H_{16}Br_2N_2O_2S$: C, 34.94; H, 3.9. Found: C, 34.90; H, 3.88.

4.2. Procedure for the addition of acetone to *trans*-β-nitrostyrene catalyzed by 1a–i, 2, and 3a–e

A mixture of *trans*-β-nitrostyrene (0.090 g, 0.6 mmol), organocatalyst (0.15 mmol), acetone (0.5 mL, 6 mmol), and toluene (2 mL) in a 25 mL flask was stirred at room temperature for

120 h. After the evaporation of the solvent under vacuum, the residue was separated by flash chromatography over silica gel (dichloromethane) to give (*S*)-5-nitro-4-phenylpentan-2-one as a white solid. The enantiomeric excess was determined by HPLC with *Chiralpak AS-H* column at 208 nm (hexane/*i*-PrOH 75:25, 1 mL/min); $t_{R(\text{major})}$ = 13.7, $t_{R(\text{minor})}$ = 19.1 min.

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